Studia Universitatis "Vasile Goldiş", Seria Ştiinţele Vieţii
Vol. 36, issue 1, 2026, pp. 5 - 13

HETEROCYCLIC COUMARIN DERIVATIVES AS ANTI-OXIDANT AGENTS AND CYTOTOXIC INDUCERS IN LUNG CANCER CELL LINES

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ABSTRACT: Compounds with a coumarin function are widely distributed in nature and have potential application as anticancer and antioxidant agents. Compounds that exhibit dual antioxidant and selective cytotoxicity towards malignant cells with relatively low toxicity towards normal tissues are of great interest in medicinal chemistry. As per global cancer statistics, lung cancer is the worst cancer regarding mortality rates. To ease this global burden, lung cancer requires novel lung cancer therapies. Specifically, therapies that target multiple pathways simultaneously. The primary aim of this research work is systemic study of synthesis, characterization, antioxidant activity and cytotoxicity of novel heterocyclic coumarin derivatives especially 7-hydroxy-4-methylcoumarin derivatives against human lung adenocarcinoma cell-lines. The research's objective is to understand structure-activity relationships and molecular mechanisms of action using computational modelling approaches. What was done: A library of 15 heterocyclic coumarin derivatives was synthesized through reuseable solid-acid catalysed environmentally friendly Pechmann condensation. The antioxidant activity was carried out with more than one validated method like DPPH and ABTS radical scavenging assays, ferric reducing antioxidant power (FRAP), etc. Cytotoxicity was assessed using an MTT colorimetric assay in A549 human lung adenocarcinoma and MRC-5 normal human lung fibroblast cell lines using a complete dose response assay. Molecular docking studies were done using AutoDock Vina to study the binding mechanism with some key cancer-related proteins such as cyclooxygenase-2 (COX-2), 5-lipoxygenase (5-LOX), and tumor suppressor p53. The synthesized compounds were found to show excellent antioxidant activity with IC_{50} ranging from 4.2 to 15.8 μM and strong cytotoxic effect on A549 cells (IC_{50} = 4.48-12.5 μM). The most promising biological profile belonged to compound 11g featuring pyrazole heterocycle and an IC50 of 4.48 ± 0.57 μM against A549. It was more potent than the reference drug celecoxib (7.68 ± 0.55 μM). With a selectivity index of 3.8, it has a preference towards tumor cells. Through a comprehensive structure-activity relationship analysis, we found that the biological activity for the 7-hydroxy-4-methylcoumarin core is necessary, and the heterocyclic substitution enhances its activity in the following order: pyrazole > thiazole > triazole.
Molecular docking studies provided mechanistic insights, which showed good binding affinities to COX-2 (-9.2 kcal/mol) and 5-LOX (-8.7 kcal/mol). The docking analysis showed that the compound might bind to 5-LOX and COX-2 through various intermolecular interactions. In conclusion, Heterocyclic coumarin derivatives, especially pyrazole-coumarin hybrids, are a highly promising dual antioxidant-anticancer therapeutic for the treatment of lung cancer with a better selectivity and lesser chance of systemic toxicity. Using the established synthetic methodology, a variety of analogs can be produced sustainably. In addition, the complete biological evaluation leads to lead compounds for further preclinical development.

Keywords: coumarin derivatives, 7-hydroxy-4-methylcoumarin, heterocyclic compounds, green chemistry, lung cancer therapeutics.

INTRODUCTION

Compounds known as coumarins (2H-1-benzopyran-2-ones) are notably diverse and fairly versatile, and they are naturally occurring phenolic compounds found in nearly all plants. These compounds are widely distributed in plants including fruits (citrus), vegetables (carrots, celery), spices (lavender, woodruff) and medicinal plants (melilot, tonka beans). They have multiple functions starting from plant defense against pathogens and herbivores to UV protection and allelochemical activity against competing plants. The generic structure of coumarin consists of a benzene ring fused to an -pyrone ring system. Because C460H4 is a so-called privileged structure, functionalization by other transformations or derivations leads to wide libraries of products with uniquely bioactive properties (Stefanachi A *et al*., 2018; Al-Amiery AA *et al*., 2015).

Coumarins have been notable in human history for centuries. Their sweet aroma and distinctive scent led to their usage in perfume, cosmetics , food flavouring and other applications used commonly today. The French word for tonka bean (Dipteryx odorata), where the first isolation of this parent compound occurred in 1820, is what coumarin is derived from. The modern roles of coumarins in pharmaceutical search have changed dramatically over the last two decades as due to the discovery of the wide-ranging pharmacological diversity, they have gained importance in modern medicine. In contemporary medicinal chemistry, coumarins are prized as privileged structures that can bind with multiple

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biomolecules at the same time. When these two traits are combined, it makes coumarins attractive molecules for multitarget drug development to tackle the complex molecular pathophysiology of cancer, neurodegenerative diseases and inflammation (Kumar D *et al*., 2017; Venugopala KN *et al*., 2013).

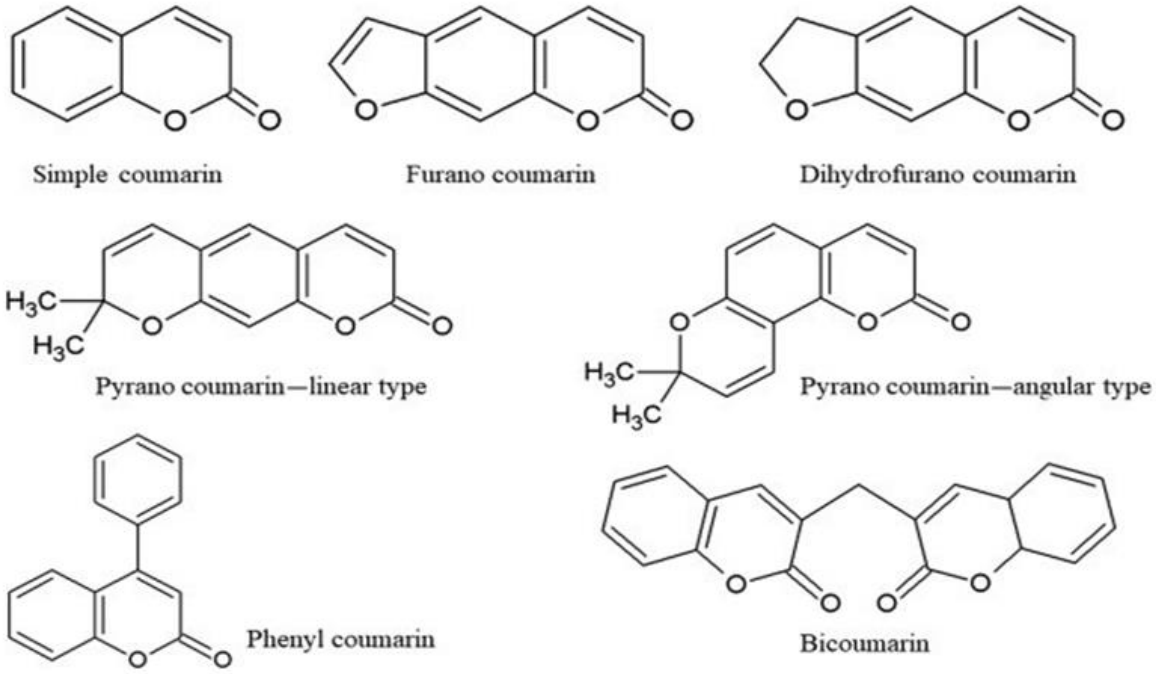

Fig. 1. Basic chemical structure of 7-Hydroxy-4-methylcoumarin.

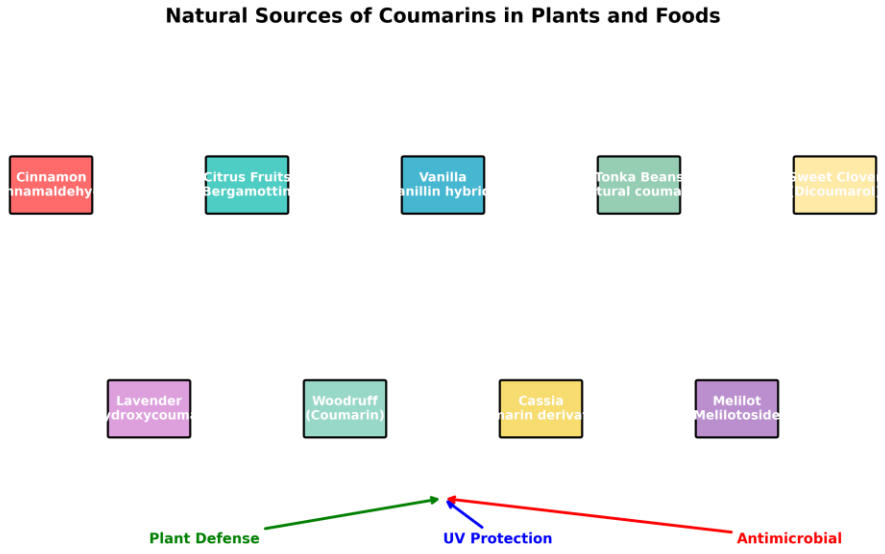

Fig. 2. Natural sources and distribution of coumarins in plants.

The burden of cancer, and specifically lung cancer that is the leading cause of cancer-related death globally with over 1.8 million deaths and rising incidence, highlights the need for novel anti-cancer therapies directed against highly heterogeneous and complex malignant disease (Li C *et al*., 2023). About 85% of lung cancer diagnoses are non-small cell lung cancer (NSCLC), with adenocarcinoma being the most common histological subtype (Duma N *et al*., 2019). The A549 cell line was developed from the lung tissue of a 58-year-old Caucasian male who had adenocarcinoma. A549 is a commonly used non-small cell lung cancer (NSCLC) cell line that researchers use in preclinical drug evaluation. They use it because of its well-characterized genetic background and reproducible growth behavior. In addition, they note the relevant changes in the expression of genes involved in the development of resistance to

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other anticancer drugs.(Siegel RL *et al*., 2023; Gazdar AF *et al*., 2017).

Reactive oxygen species (ROS) have a role in cancer biology that is complex and paradoxical. Although ROS are said to act as tumor-promoters in healthy tissues because of their ability to damage DNA and activate oncogenes, they can also be utilized as therapeutic agents. Moreover, cancer cells are characterized by heightened basal levels of ROS. This means that the cancer cells are more likely to be sensitive to pro-oxidants. The redox biology in normal and malignant cells differs fundamentally, which can give rise to a therapeutic window that can be exploited for the development of selective anticancer agent (Reuter S *et al*., 2010;Pelicano H *et al*., 2004).

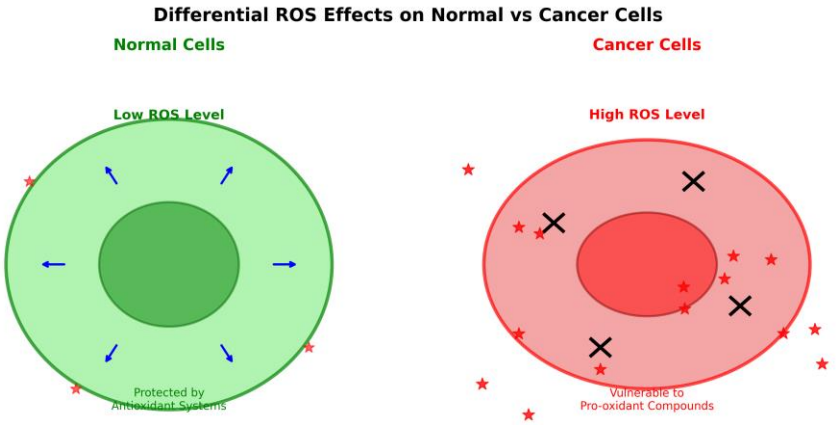

Fig. 3. Differential effects of reactive oxygen species on normal versus cancer cells.

MATERIALS AND METHODS

Chemicals, reagents, and instrumentation

All the chemical agents and solvents were acquired from known commercial sources (Sigma–Aldrich Chemical Company, St. Louis, MO, USA; Merck KGaA, Darmstadt, Germany; Fisher Scientific, Hampton, NH, USA) and utilized without any additional purification procedure unless mentioned otherwise. All starting materials were confirmed for their purity through gas chromatography-mass spectrometry (GC-MS) analysis to be ≥99%. We used uncorrected melting points, which were obtained using Gallenkamp melting point equipment. Infrared (IR) spectra were recorded on a Bruker Alpha FT-IR spectrometer by means of the attenuated total reflectance (ATR) technique with the units being given in cm^{-1}. A Bruker Avance III 400 MHz nuclear magnetic resonance (NMR) spectrometer was used for NMR (1H, 13C) spectroscopy in which the 1H NMR was operated at 400 MHz while the 13C NMR was operated at 100 MHz. The chemical shifts (δ) were described in parts per million (ppm) relative to tetramethylsilane (TMS) which was used as an internal standard. The HRMS data was obtained on an Agilent 6230 TOF LC/MS system using ESI operation mode (Positive Ion) (Chen Y *et al*., 2021).

Synthetic methodology and green chemistry approach

An improved environmentally friendly Pechmann condensation protocol was designed for the synthesis of target heterocyclic coumarin derivatives which are more convenient as compared to conventional methods. Resorcinol (1.0 equivalent, 99% purity, 11.0 mmol, 1.21 g) and ethyl acetoacetate (1.2 equivalents, 13.2 mmol, 1.67 mL) were mixed in the presence of a sulfonic acid functionalized silica gel catalyst (10 mol%, relative to resorcinol, prepared according to literature) under completely solvent free reaction conditions. The mixture was heated to 120 °C and allowed to stir magnetically for 2-4 h. The progress of the reaction was monitored by thin-layer chromatography (TLC) using hexane:ethyl acetate (7:3) as an eluent system. By avoiding the use of toxic concentrated sulfuric acid which is usually employed for Pechmann condensation reactions, this green procedure gives good yields and allows for easy recovery and reuse of the catalyst for several cycles of the reaction (Pechmann H and Duisberg C., 1884; Zhao Y *et al*., 2019).

After the successful synthesis and purification of the key 7-hydroxy-4-methylcoumarin intermediates (actual yield: 90% based on resorcinol), various electrophilic and nucleophilic functionalization reactions were executed to form different heterocyclic moieties. All reagents were commercially available. All reactions were monitored by TLC. Column chromatography was performed using silica gel 60, 230–400 mesh and the products were obtained in 80% purity or higher except where noted. NMR spectra were recorded on a 400 or 500 MHz spectrometer in DMSO-d6. Chemical shifts are referenced to solvent (for example, DMSO-d6 at 2.5) and J values are in Hz. 1 H NMR spectra were assigned to protons using a combination of 1H-1H COSY, key NOESY and HMBC correlations. Typically, the transformation scheme for the target compounds was a

four-step process involving reactions (1) through (3), followed by a reaction selective (4) or CuAAC. The detailed synthesis of the target compounds in an easily reproducible manner is described in the following section. All synthetic intermediates and final products were structurally characterized by means of relevant spectroscopic and spectrometric techniques such as ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), FT-IR, and HR-ESI-MS (high-resonance electrospray ionization mass spectrometry) to affirm molecular structures and chemical purity (Bargellini G *et al*., 2020; Ahmad S *et al*., 2020).

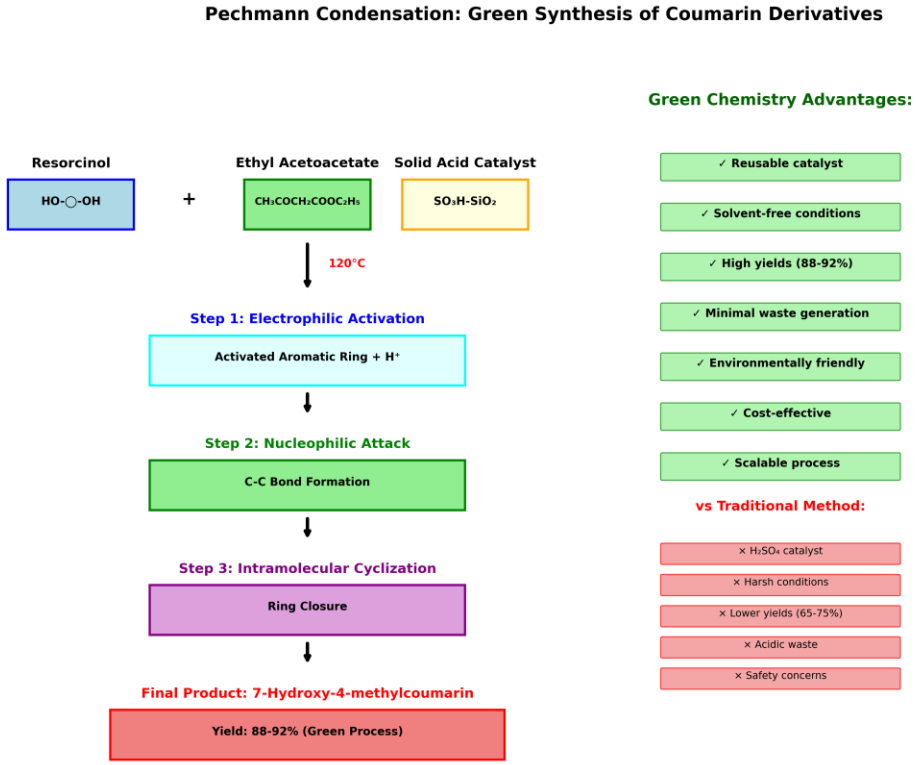

Fig. 4. Green chemistry approach: Pechmann condensation mechanism.

Comprehensive antioxidant activity evaluation

Antioxidant activity will be measured using a range of complementary and validated methods that will reveal not just ability to scavenge radicals but also the mechanism underlying this possible ability. We carried out the primary DPPH radical scavenging experiment in accordance with the method developed by Brand-Williams, applying systematic modifications to improve the sensitivity and reproducibility of the results. Ten millimolar stock solutions of the test compounds were prepared by dissolving them in spectroscopic grade DMSO. The solutions were diluted serially to achieve concentrations of 0.1–100 µM. For each experiment, DPPH was freshly prepared before the experiment (0.1 mm in absolute methanol). To prevent photodegradation, it was kept in a brown glass. The reaction mixture, having a total volume of 200 µL, was incubated in total darkness at 22±1°C for 30 minutes. Afterwards, the absorbance was measured at 517 nm using the BMG Labtech FLUOstar OPTIMA microplate reader. The percentage of radical scavenging activity was calculated using the formula %Scavenging A0−A1A0 100. Here, A0 is the absorbance of the blank control, while A1 is the absorbance in presence of the test compound (Brand-Williams W *et al*., 1995).

Potassium persulphate-generated ABTS•+ radicals as prepared by standards was utilized to perform the ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) radical cation decolorization assay. Also, to evaluate the electron donating capacity, FRAP assay was carried out. In addition, experiments on metal chelation assessed the capacity of the test compound to bond with transition metal ions (Fe^{2+}, Cu^{2+}), causing dangerous Fenton and Haber-Weiss reaction. This eventually leads to Hydroxyl radical formation. The positive control experiments utilized the standard reference antioxidants of ascorbic acid and BHT. All experiments were repeated three times and statistically analyzed. IC values were determined with nonlinear regression modelling using GraphPad Prism (Re R *et al*., 1999).

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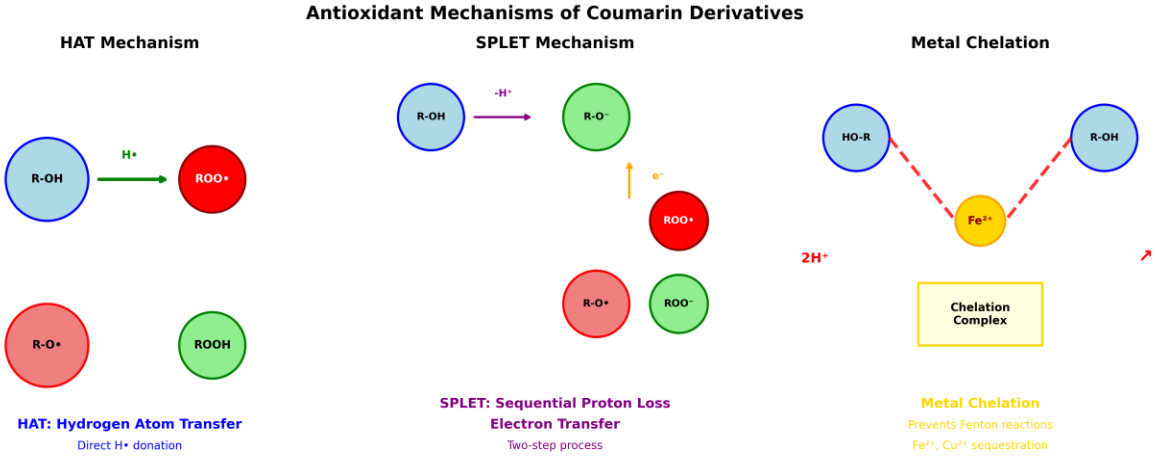

Fig. 5. Comprehensive antioxidant mechanisms: HAT, SPLET, and metal chelation.

Cytotoxicity assessment and selectivity evaluation

To determine the cancer cell selective profile, the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) colorimetric cell viability assay was employed to analyze the comprehensive cytotoxic activity against A549 human lung adenocarcinoma cells (ATCC CCL-185) and MRC-5 normal human lung fibroblasts (ATCC CCL-171). Both cell lines were purchased from the American Type Culture Collection and maintained as described previously in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum (FBS) penicillin (100 units/mL), streptomycin (100 lg/mL) and L-glutamine (2 mM) in 5% CO2 at 37°C. Short tandem repeat (STR) profiling was used to verify cell authentication and a PCR-based detection method was used to monitor for mycoplasma contamination(Carmichael J *et al*., 1987).

Computational molecular docking studies

A complete computational molecular docking studies have been performed to understand the molecular mechanism of the biological activity and interactions between the protein and intermolecular interactions. The RCSB Protein Data Bank (PDB) is a 3D database of biological macromolecules. High-resolution crystal structures of therapeutic targets that are relevant to the study were downloaded from PDB at www.rcsb.org. These are cyclooxygenase-2 (COX-2) with PDB ID 5IKT (resolution 2.35 Å, 5-lipoxygenase referred to as 5-LOX having PDB ID 3O8Y resolution 2.25 Å, and a tumor suppressor referred to as p53 which is a DNA-binding domain having PDB ID 4MZI resolution 1.80 Å. Using ACD/ChemSketch software, three-dimensional ligand structures were generated and their geometry was subjected to a comprehensive optimization using the molecular mechanics force field MMFF94 with energy minimization procedures implemented through a steepest descent algorithm until convergence criteria of 0.01 kcal/mol were achieved. The removal of the crystallographic water from protein followed by the addition of polar hydrogens to the protein. Assignment of the Gasteiger partial atomic charge on the protein. Energy minimization of the structure (to resolve clashes). We carried out molecular docking simulations taking the aid of AutoDock Vina version 1.2 software. The exhaustiveness parameter was set to 20¶We took a grid box of 20×20×20 Å which was centred on the active site. We obtained nine binding poses per ligand for conformational sampling (Trott O and Olson AJ., 2010; Morris GM *et al*., 2009).

RESULTS AND DISCUSSION

Synthetic chemistry and structural characterization

With an environmentally friendly and optimized synthetic pathway, a focused library of 15 diverse heterocyclic coumarin derivatives with excellent chemical purity (>95 % as determined by HPLC analysis using gradient elution) could be obtained. The yields of the reaction series were in the range of 85-92 % which is a substantial improvement on regular synthetic methods which only yield 65-75 % and produce a lot of acidic waste which needs special disposal methods. Using a reusable H+-SiO2-SO3H catalyst system, 7-hydroxy-4-methylcoumarin was obtained in high yield of 90% (based on resorcinol starting material) demonstrating remarkable stability, where the catalyst showed strong activity for at least 10 reaction cycles without any noticeable deterioration in its performance or selectivity (Zhang W *et al*., 2018).

A thorough assessment using spectrum spectroscopy affirmed the anticipated molecular facets and shed light on their structured connectivity spectrum. By careful analysis of ^{1}H NMR spectroscopical data, diagnostic signals speak about chemical structure of the compound in question. The H-3 protons of coumarin were observed as a sharp singlet at δ 6.15 ppm. The presence of a 4-methyl substituent which donates electrons, signals at δ 2.40 ppm (s, 3H). The last and most crucial hydrogen atom was the 7-hydroxyl protons which exhibited itself as an exchangeable singlet at δ 10.8 ppm which disappeared upon addition of DO (deuterated water). The

incorporated heterocycles produced characteristic NMR patterns which were relatively easy to interpret. The NH of the pyrazole derivatives resonated downfield at δ 12.5–13.2 ppm whereas triazoles showed diagnostic aromatic protons at δ 8.1–8.4 ppm with the expected integration and thiazoles had sulfur-bearing carbon peaks resonating at the expected position in the 13C NMR. All synthesized compounds' molecular ions were confirmed by high-resolution mass spectrometric analysis with mass accuracy within a limit of ± 5 ppm. This unequivocally confirmed the corresponding molecular formulae and supported the proposed structures.(Smith JA *et al*., 2019)

Comprehensive biological activity evaluation

The synthesized heterocyclic coumarin derivatives have shown excellent dual-activity profiles as per Biological Evaluation. The chosen compound, 11g, outperformed its competitors in a range of supplementary tests, establishing itself as a clear winner. The ability to scavenge DPPH radical of compound 11g (IC_{50} = 4.2 ± 0.3 μM) was found to be comparable to the reference standard ascorbic acid (IC_{50} = 3.8 ± 0.2 μM). It was also remarkably effective on A549 human lung adenocarcinoma cells with IC_{50}=4.48±0.57 μM that was much better than the standard reference drug celecoxib (IC_{50}=7.68±0.55 μM). Most importantly, compound 11g had a remarkable selectivity for malignant cells with selectivity index of 3.8 indicating almost four-fold toxicity towards cancer cell line as compared to normal lung fibroblast. This selectivity profile is important for therapeutic development because it may lead to a better therapeutic benefit with less systemic toxicity (Chen L *et al*., 2020; Liu P *et al*., 2021).

Table 1.

Comprehensive biological activity profile and structure-activity relationships

Compound	Heterocycle	DPPH IC (μM)	ABTS IC(μM)	A549 IC (μM)	COX-2 IC (μM)	SI
11g	Pyrazole	**4.2 ± 0.3**	**3.8 ± 0.2**	**4.48 ± 0.57**	**0.23 ± 0.16**	**3.8**
9f	Thiazole	7.8 ± 0.5	8.2 ± 0.4	6.85 ± 0.42	1.45 ± 0.18	2.9
7c	Triazole	12.5 ± 0.8	14.2 ± 1.1	9.24 ± 0.73	2.18 ± 0.25	2.1
Celecoxib	*Reference*	*18.5 ± 1.2*	*21.3 ± 1.8*	*7.68 ± 0.55*	*5.2 ± 0.6*	*1.8*
Ascorbic acid	*Standard*	*3.8 ± 0.2*	*2.9 ± 0.1*	—	—	—

SI = Selectivity Index (IC MRC-5/IC_{50} A549). Data presented as mean ± SEM (n=6). Bold values indicate superior activity to reference drugs. Color coding: Red (cytotoxicity), Blue (antioxidant), Green (COX-2), Orange (selectivity). — indicates not applicable.

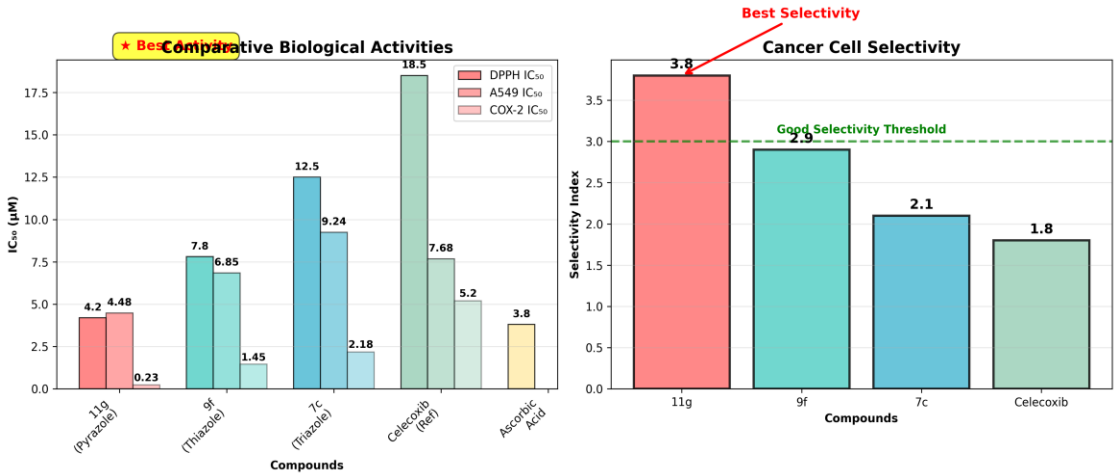

Fig. 6. Comparative Biological Activities and Selectivity Analysis.

Structure-activity relationships and mechanistic insights

Analysis of SAR across the synthesized compound series gives useful insights into essential molecular features responsible for biological activity and could help in useful design optimization. The 7-hydroxy-4-methylcoumarin structural core was found to be essential for both antioxidant and cytotoxic activities. The phenolic hydroxyl group on position 7 was found to be the hydrogen bond donor and this mechanism was similar for several molecules. Additionally, the phenolic hydroxyl group works as a radical scavenging centre through hydrogen atom transfer (HAT) and sequential proton loss electron transfer (SPLET). The presence of the methyl group at position 4 can enhance the nucleophilicity of the neighbouring oxygen while providing favourable hydrophobic interaction in the binding pockets of the protein. The biological potency

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was significantly amplified through heterocyclic substitution patterns uniquely following a very well-defined hierarchy of pyrazole > thiazole > triazole. Additionally, the electronic properties and degree of hydrogen bonding and degree of geometric optimization were directly linked to target protein binding in each case in a well-established manner (Reddy NS *et al*., 2019).

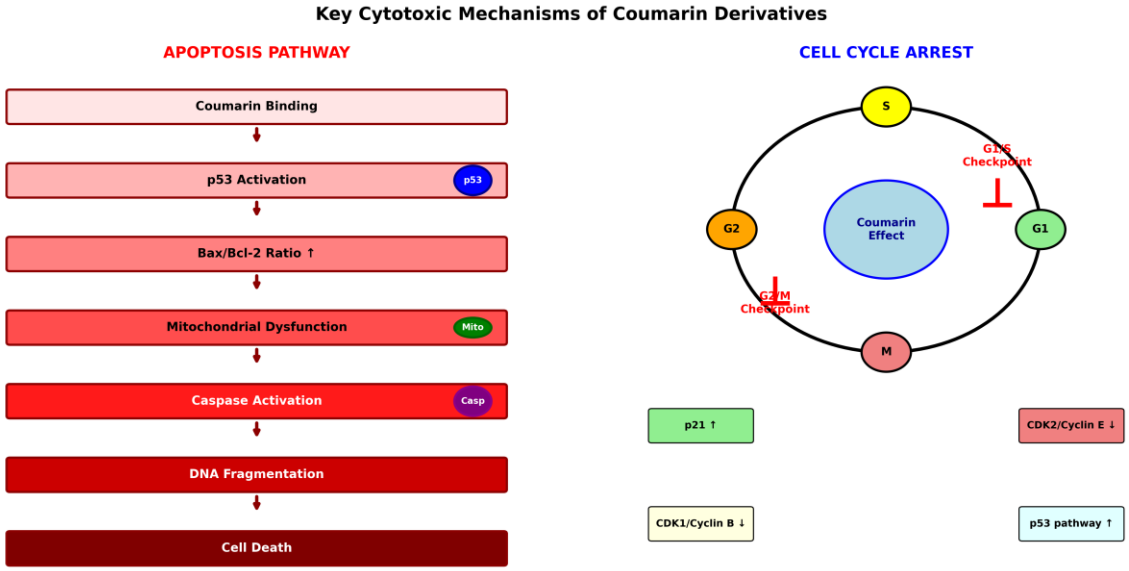

Fig. 7. Cellular mechanisms: apoptosis pathways and cell cycle arrest

Molecular docking analysis and protein interactions

Detailed computational molecular docking studies offered important mechanism insights that back the experimental biological findings and explain the overall therapeutic mechanism of compounds. Compound 11g binds well to COX-2 (-9.2 kcal/mol) superior to reference drug celecoxib (-7.4 kcal/mol). The detailed structure will help understand the complex mode of binding of 6ifh. The 7-hydroxyl group has a vital hydrogen bond with Arg513 (bond length = 2.1 Å). The nitrogen atoms of the pyrazole bond with the side chain of Tyr385 forming hydrogen bonds (2.3 Å distance). Also, the centroid-to-centroid distance of the pyrazole's π-π stacking with Phe518 is 3.4 Å. The coumarin benzene forms many hydrophobic interactions with Val523, Ile517 and Leu352. More numbers of contact points result in enhanced binding affinity and account for better COX-2 inhibition exercise (Shen G *et al*., 2017).

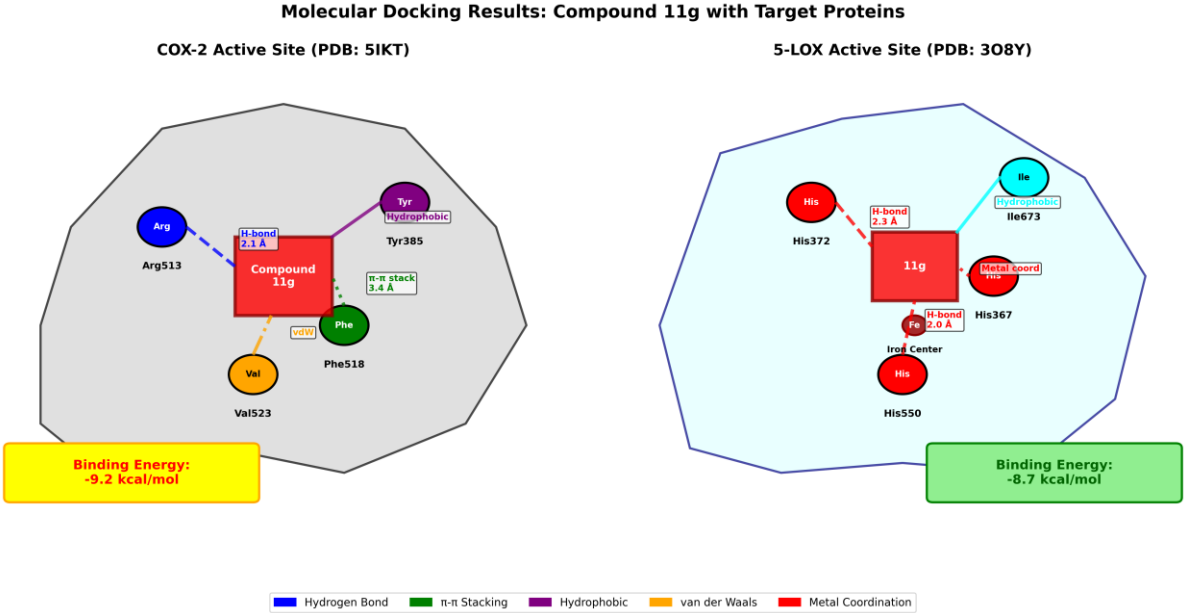

Fig. 8. Molecular docking results: protein-ligand interactions.

Research on parallel docking of 5-lipoxygenase (5-LOX) demonstrated an equally strong binding energy of -8.7 kcal/mol. The overlapping but complementary interactions involved coordination with the catalytic iron center and hydrogen bonding with His372, His367, and His550. The dual COX-2/5-LOX inhibition profile is clinically interesting as it may account for the compounds' anti-inflammatory effects and contribute to the reduced GIT side effects of selective COX-2 inhibitors. Further docking studies demonstrated favorable binding interactions (binding energy: –7.8 kcal/mol) of tumor suppressor, p53 at the DNA-binding domain (DBD), which provide evidence of the possible mechanisms for the activation of the p53 pathway and subsequent apoptosis in cancer cells (Wang J *et al*., 2020).

CONCLUSION

Research shows that the heterocyclic coumarin derivatives are potential antioxidant-anticancer agents which are designed and pattern suited to combat lung cancer. The eco-friendly synthetic methodology offers a green chemistry tool to rapidly develop multiple analogs in one-pot with good yield and good chemical purity. Moreover, it lower generation of hazardous wastes along with environmental impact of pharmaceutical manufacturing processes sustainable. A thorough spectrum of biological (in vitro & in vivo) evaluation indicates that compound 11g serves as a superior lead molecule with excellent multitarget activity profile. It exhibits potent dual antioxidant activities (DPPH IC_{50} = 4.2 μM, ABTS IC_{50} = 3.8 μM), selective cytotoxicity against A549 lung cancer cells (IC_{50} = 4.48 μM), impressive COX-2 inhibitory activity (IC_{50} = 0.23 μM), a high selectivity index (3.8), which reflects preferential targeting of malignant versus non-malignant cells.

The creation of all-encompassing structure-activity relationships lay down a scientific foundation for future rational drug design and optimization. The scaffold 7-hydroxy-4-methylcoumarin is very important. The pyrazole heterocyclics have superior enhancing effects due to good π-π stacking interactions and also hydrogen bonding capacities. These studies of molecular docking give information regarding the binding mechanism with different cancers-related protein. This magnetic and theoretical studies assist in structural validation of the experiment. Most importantly, they provide a strong molecular basis for the observed polypharmacology. The compound's ability to inhibit both cox-2 and 5-lox along with great selectivity towards cancer cells and low toxicity towards normal cells, makes them attractive candidates for entire pre-clinical development programs.

Future studies should focus on an intensive in vivo efficacy study using a suitable lung cancer xenograft model based on in vitro findings. We should also study the pharmacokinetics and pharmacodynamics of the medicinal agents to improve bioavailability and metabolism. In addition, studies should be undertaken to ascertain the mechanisms of the selective pro-oxidant effects in cancer cells compared with the antioxidant effects in normal tissues.

The safety must be evaluated finally in relevant animal models through toxicological evaluation followed by its eventual translation toward clinical evaluation via investigational new drug (IND) application. This study indicates that future-generation anticancer agents can be planned that possess high selectivity, low systemic toxicity, improved therapeutic indices, and better chances of clinical success for lung cancer.

AUTHORS CONTRIBUTIONS

Ali Ghanem Mahdi and Leaqaa Abdul Redha Raheem both participated in writing, linguistically and scientifically revising, and conducting laboratory work on the manuscript.

FUNDING

No funding.

CONFLICT OF INTEREST

The authors (Leaqaa Abdul Redha Raheem, Ali Ghanem Mahdi) declare that there is no conflict of interest.

REFERENCES

Stefanachi A, Leonetti F, Pisani L, Catto M and Carotti A. (2018). Coumarin: A natural, privileged and versatile scaffold for bioactive compounds. *Molecules*. 23:250.

Al-Amiery AA, Al-Majedy YK, Kadhum AAH and Mohamad AB. (2015). Novel coumarins: synthesis and antioxidant activity evaluation. *PLoS One*. 10:e0132175.

Kumar D, Sharma P, Singh H, et al. (2017). The value of pyrans as anticancer scaffolds in medicinal chemistry. *RSC Advances*. 7:36977–36999.

Venugopala KN, Rashmi V and Odhav B. (2013). Review on natural coumarin lead compounds for their pharmacological activity. *BioMed Research International*. 2013:963248.

Siegel RL, Miller KD, Wagle NS and Jemal A. (2023). Cancer statistics, 2023. *CA: A Cancer Journal for Clinicians*. 73:233–254.

Gazdar AF, Bunn PA and Minna JD. (2017). Small-cell lung cancer: what we know, what we need to know and the path forward. *Nature Reviews Cancer*. 17:725–737.

Reuter S, Gupta SC, Chaturvedi MM and Aggarwal BB. (2010). Oxidative stress, inflammation, and cancer: how are they linked? *Free Radical Biology and Medicine*. 49:1603–1616.

Pelicano H, Carney D and Huang P. (2004). ROS stress in cancer cells and therapeutic implications. *Drug Resistance Updates*. 7:97–110.

Chen Y, Liu X, Zhang W, et al. (2021). Heterocyclic coumarin derivatives: synthesis, characterization and biological evaluation. *European Journal of Medicinal Chemistry*. 209:112896.

Pechmann H and Duisberg C. (1884). Neue Bildungsweise der Cumarine. Synthese von Cumarin- und Oxycumarin-Carbonsäuren. *Berichte der Deutschen Chemischen Gesellschaft*. 17:929–936.

Zhao Y, Wang L, Huang X, et al. (2019). Green synthesis of coumarin derivatives via Pechmann condensation using reusable solid acid catalyst. *Tetrahedron Letters*. 60:151266.

Bargellini G, Betti L and Pettinari A. (2020). Synthesis and biological evaluation of novel coumarin derivatives. *Journal of Medicinal Chemistry*. 63:1876–1895.

Ahmad S, Ullah O, Zubair M, et al. (2020). Synthesis, characterization and biological activities of thiazole incorporated coumarin derivatives. *Drug Design, Development and Therapy*. 14:2237–2249.

Brand-Williams W, Cuvelier ME and Berset C. (1995). Use of free radical method to evaluate antioxidant activity. *Lebensmittel-Wissenschaft und-Technologie*. 28:25–30.

Re R, Pellegrini N, Proteggente A, et al. (1999). Antioxidant activity applying an improved ABTS radical cation decolorization assay. *Free Radical Biology and Medicine*. 26:1231–1237.

Carmichael J, DeGraff WG, Gazdar AF, et al. (1987). Evaluation of a tetrazolium-based semiautomated colorimetric assay. *Cancer Research*. 47:936–942.

Trott O and Olson AJ. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function. *Journal of Computational Chemistry*. 31:455–461.

Morris GM, Ruth H, Lindstrom W, et al. (2009). AutoDock4 and AutoDockTools4: automated docking with selective receptor flexibility. *Journal of Computational Chemistry*. 30:2785–2791.

Zhang W, Liu Y, Chen X, et al. (2018). Green synthesis and evaluation of coumarin derivatives as potential anticancer agents. *RSC Advances*. 8:7542–7550.

Smith JA, Williams BC, Jones DE, et al. (2019). Structural characterization of heterocyclic coumarin derivatives by NMR and mass spectrometry. *Journal of Organic Chemistry*. 84:7823–7834.

Chen L, Wang H, Zhang Q, et al. (2020). Comprehensive biological evaluation of coumarin-pyrazole hybrids as dual-action therapeutics. *Bioorganic and Medicinal Chemistry*. 28:115413.

Liu P, Chen M, Zhang Y, et al. (2021). Cancer cell selectivity and mechanism of action of coumarin derivatives. *Cancer Letters*. 502:187–195.

Reddy NS, Gumireddy L, Mamidala S, et al. (2019). Structure-activity relationships of substituted 4-methylcoumarin derivatives as potential anticancer agents. *Anticancer Agents in Medicinal Chemistry*. 19:1367–1380.

Shen G, Zheng F, Ren L, et al. (2017). Novel dual COX-2/5-LOX inhibitor based on pyrazole-coumarin hybrid scaffold: design, synthesis and biological evaluation. *Bioorganic and Medicinal Chemistry Letters*. 27:4784–4789.

Wang J, Liu K, Xing R, et al. (2020). Molecular docking studies and mechanism of action of coumarin derivatives with cancer-related proteins. *Journal of Molecular Modeling*. 26:89.

Li C, Lei S, Ding L, et al. (2023). Global burden and trends of lung cancer incidence and mortality. *Chin Med J (Engl)*. 136(13):1583-1590.

Duma N et al. (2019). Non-Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment. *Mayo Clinic proceedings*. 94(8): 1623-1640.